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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/147,693	02/17/99	LUBITZ W	P564-9005

HM12/0302
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EXAMINER	
SANDALS,W	
ART UNIT	**PAPER NUMBER**
1636	7

DATE MAILED: 03/02/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/147,693	Applicant(s) Lubitz et al.
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Jan 18, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *38-76* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *49* is/are allowed.

☒ Claim(s) *38-48 and 50-76* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Arguments

1. Amendments to the claims in Paper No. 5, filed December 12, 1999 has overcome the rejections of claims 1-3, 6-13, 15-30 and 34-37 under 35 USC 112, second paragraph in the previous office action, and the rejection is withdrawn.

2. Arguments filed in Paper No. 5 regarding the rejection of claims 1-20 under 35 USC 103(a) have been fully considered and are found persuasive. As a result, new grounds of rejection are contained in the rejection below.

3. Arguments regarding claims 29, 30, 36 and 37 in Paper No. 5 under 35 USC 112, first paragraph in the previous office action as they pertain to new claims 63-65, 71 and 72, have been considered but are not found persuasive. The rejection is repeated below along with a response to the arguments.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 63-65, 71 and 72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims recited broadly encompass any bacterial live or ghost cell as a vaccine and a method of use.

The specification provides insufficient guidance of how to make and use a bacterial live or ghost cell as a vaccine. It is well recognized in the art that is unclear whether an antigen, in this case a live or ghost bacterial cell, will elicit protective immunity. Ellis, R. W. (see Chapter 29 of "VACCINES" [Plotkin, S. A. et al., (ed.), published by W.B. Saunders Company (Philadelphia) in 1988, see especially page 571, second full paragraph] exemplifies this problem in the recitation that "[t]he key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies...and thus protect the host against attack by the pathogen".

Since:

1. no working examples are set forth in the specification of the protein useful for vaccination; and

2. the art teaches the unpredictability of using an antigen for vaccination,

it would be an undue burden and be unpredictable for a skilled artisan to make and use a vaccine comprising live or ghost bacterial cells as broadly claimed.

Response to Arguments

Paper No. 5 and the Supplemental Response of Paper No. 6, filed January 18, 2000 have asserted that since bacterial live cells and bacterial ghosts have been used to produce vaccines, that the **use** of bacterial ghosts has been established for vaccine production. While it is true that bacterial ghosts have been used to produce vaccines, it does not affect the grounds of enablement as set forth above. The key to successful vaccine making is to identify that a particular antigen will produce a protective immunity by vaccination with a particular carrier and/or adjuvant. The instant claimed invention does not provide teachings which demonstrate the general ability to make a vaccine with a bacterial cell or ghost bacterial cell and **any** antigen produced by recombinant methods in the bacterial cell which will in fact produce the desired protective immunity in a subject animal. The rejection above makes it clear that no such evidence has been set forth in the instant claims or specification to enable the claims as written.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 38-42, 44-48, 50, 52-62, 66-70 and 73-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eliason et al. in view of Pakula et al., Benson et al. and Zacharias et al.

The claims are drawn to a method for selecting mutated O_R or O_L operator DNA sequences from lambdoid phages which have different thermostability compared to wild-type sequence with regard to binding a repressor wherein the operator DNA sequence is subjected to mutation and selected for different thermostability from the wild type with respect to binding of a repressor. The repressor may be cI857, and the thermostability may be increased from 3-10° or 7-9°. The claims are also drawn to the mutated O_R or O_L operator DNA sequences from lambdoid phages which may be incorporated into a vector, and to a host bacterial cell.

Eliason et al. taught (see especially the abstract, the introduction, page 2342 and the tables and figures) a method for selecting mutated O_R or O_L operator DNA sequences from lambdoid phages which have different binding compared to wild-type sequence with regard to binding a repressor wherein the operator DNA sequence is subjected to mutation and selected for different binding from the wild type with respect to binding of a repressor. Eliason et al. also taught mutated O_R or O_L operator DNA sequences from lambdoid phages which may be incorporated into a vector, and to a host bacterial cell.

Eliason et al. did not teach that the repressor may be cI857, and the thermostability may be increased from 3-10° or 7-9°.

Pakula et al. taught (see especially the abstract, introduction and the discussion) the change in thermal stability of a mutated repressor protein with the lambda operator. Pakula et al. discuss in great detail, the importance of the contact bases in the operator, and the manner in which they interact with the amino acids of the repressor protein. From their discussion, it is

clear that the increased thermal stability of the binding of the repressor protein is directly related to the thermodynamics of the molecular interaction between the contact bases of the operator DNA sequence and the contact amino acids of the repressor protein. Pakula et al. taught that one of skill in the art would be able to select mutated sequences in the repressor protein which would have greater binding affinity for the operator sequences and therefore higher thermostability.

Benson et al. taught (see especially the abstract, the introduction, page 26, column 1, and Page 28, column 1) the relative affinity of the lambda repressor protein for the lambda operator sequence, where the operator sequence has been mutated. Benson et al. show that the operator sequence was mutated to produce a mutant operator sequence which has greater affinity for the lambda repressor protein than the wild type operator sequence.

Zacharias et al. taught (see especially the abstract, the introduction and the conclusion) the mutation of the lambda operator sequence to produce a mutated operator sequence which has a higher affinity for the lambda repressor sequence.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant invention to combine the mutated DNA lambda operator sequences of Eliason et al. or Benson et al. or Zacharias et al. with the increased thermostability of repressor sequences of Pakula et al. since Pakula et al. taught the increased thermostability of the repressor complex was due to changes in the thermodynamic molecular interaction of specific bases and amino acids in the binding site of the operator/repressor pair. Eliason et al. taught the changes in the operator sequence would affect the thermodynamic stability of the interaction of the operator/repressor

complex. Since cI857 is a known repressor mutant of the lambda operator, and mutations of the sequence of the cI857 would also be affected by the same thermodynamic laws which apply to the repressor/operator complexes of Eliason et al. and Pakula et al., it would have also been obvious to practice the invention with cI857.

One of ordinary skill in the art would have been motivated at the time of filing of the instant invention to combine the mutated DNA lambda operator sequences of Eliason et al. or Benson et al. or Zacharias et al. with the increased thermostability of operator/repressor binding of Pakula et al. since Pakula et al. taught in the abstract that "two suppressor substitutions increase the thermal stability of Cro by 12° C to 14° C.", and in the introduction, "two substitutions that dramatically increase the thermal stability" of the repressor complex was due to changes in the thermodynamic molecular interaction of specific bases and amino acids in the binding site of the operator/repressor pair (see especially figure 4). Eliason et al. taught in the abstract and in the introduction that the changes in the operator sequence would affect the thermodynamic stability of the interaction of the operator/repressor complex. Since cI857 is a known repressor mutant of the lambda operator, and mutations of the sequence of the cI857 would also be affected by the same thermodynamic laws which apply to the repressor/operator complexes of Eliason et al. and Pakula et al., it would have also been obvious to practice the invention with cI857. Benson et al. taught at page 28, "[f]rom our analysis of symmetric operators, we can rank changes in the natural operators as being severely detrimental, mildly detrimental, neutral, or beneficial for the binding of repressor". Zacharias et al. stated at the

abstract "[t]hese initial calculations indicate that the approach might be a useful tool to estimate conformational and energetic effects upon mutagenesis of protein-DNA complexes". The teachings of Eliason et al. that mutation of the operator causes a change in the binding temperature of the lambda repressor to the lambda operator is confirmed and strengthened by the teachings of Benson et al. and Zacharias et al. on the effects of mutation of the lambda operator in the binding affinity of the lambda repressor with the lambda operator. This makes it obvious to one of skill in the art that mutations in the lambda operator sequence would affect the temperature of activation of the lambda repressor by changing the affinity of the lambda repressor for the lambda operator. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Eliason et al. with Pakula et al., Benson et al. and Zacharias et al.

8. Claim 51 is rejected under 35 U.S.C. 103(a) as being unpatentable over Eliason et al. in view of Pakula et al., Benson et al. and Zacharias et al. as applied to claims 38-42, 44-48, 50, 52-62, 66-70 and 73-76 above, and further in view of Vasquez et al.

The claims are drawn to the mutated lambda operator sequence and methods of use as described above, and to a construct where the sequence is in operative linkage with a suicide gene.

Vasquez et al. taught (see especially the abstract, introduction, tables and figures) a lambda operator sequence in operative linkage with a suicide gene.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant invention to combine the lambda operator sequences of Eliason et al. or Pakula et al., or Benson et al. or Zacharias et al. which were in operative linkage to an antibiotic resistance gene with the suicide gene taught by Vasquez et al. which was in operative linkage with the lambda operator sequence because Vasquez et al. taught in the abstract that the use of a suicide gene inoperative linkage with the operator gene of the construct allowed the selective expression of a desired gene such as the antibiotic resistance gene of Eliason et al., Pakula et al., Benson et al. and Zacharias et al.

One of ordinary skill in the art would have been motivated at the time of filing of the instant invention to combine the lambda operator sequences of Eliason et al., Pakula et al., Benson et al. and Zacharias et al. which were in operative linkage to an antibiotic resistance gene with the suicide gene in operative linkage with the lambda operator sequence taught by Vasquez et al. because Vasquez et al. taught in the abstract that the use of the suicide gene in the construct allowed the selective expression of a desired gene such as the antibiotic resistance gene of Eliason et al. Pakula et al., Benson et al. and Zacharias et al. Vasquez et al., at page 12, column 1 recite "[t]he *lac* operator-repressor in one of the best characterized negative control mechanisms in *E. coli*", making the use of the instant claimed operator/repressor obvious. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Eliason et al. with Pakula et al., Benson et al. and Zacharias et al. and Vasquez et al.

9. Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Eliason et al. with Pakula et al., Benson et al. and Zacharias et al. and Vasquez et al. as applied to claim 38-42, 44-48, 50, 52-62, 66-70 and 73-76 above, and further in view of WO96/06164.

The claims are drawn to the mutated lambda operator sequence and methods of use as described above, and to a construct where the mutagenesis is performed in a mutator bacterial strain.

WO96/06164 taught (see especially the abstract and the summary of the invention) a mutator bacterial strain used for the well known mutation of a desired sequence of DNA.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant claimed invention to use a mutator strain of bacteria such as the mutator strain of WO96/06164 because of the well known use of such a strain of bacteria to produce mutations in a selected DNA sequence such as the instant claimed lambda operator sequence.

One of ordinary skill in the art would have been motivated at the time of filing of the instant claimed invention to use a mutator strain of bacteria such as the mutator strain of WO96/06164 because it was well known to those of ordinary skill in the art that a mutator strain of bacteria would produce the desired mutations in a selected sequence of DNA such as the instant claimed lambda operator sequence. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Eliason et al., Pakula et al., Benson et al. and Zacharias et al. and Vasquez et al. with WO96/06164.

Allowable Subject Matter

10. Claim 49 is allowed.

Conclusion

11. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
February 22, 2000

George C. Elliott, Ph.D.
Supervisory Patent Examiner
Technology Center 1600